REMARKS AND ARGUMENTS

I. The Information Disclosure Statement

At page 3 of the Office Action, it is stated that with respect to the Information Disclosure Statement submitted on October 26, 2007, references B2, B17, C33, C34 and C60 were not considered because copies of the references were not provided. Applicants submit copies of B2, B17, C33, C34 and C60 with this response. Applicants also submit with this response a Supplemental Information Disclosure Statement that lists references that have been recently cited in prosecution of another co-pending application. Copies of the references are included herewith. Applicants respectfully request that the Examiner consider the enclosed references.

II. Patentability Arguments

A. Claim Objections

At pages 4 and 5 of the Office Action, it is requested that claim 1 be amended to correct the alleged redundancy. In response, Applicants amend claim 1 as requested in paragraphs 8A and 8B of the Office Action. Applicants respectfully submit that the amendments correct the alleged redundancy and therefore, the objections to claims 1-5 may be property withdrawn.

B. The Claim Rejections Under 35 USC §102(e) Should Be Withdrawn

1. *Ladner et al.*

At page 5 of the Office Action, the rejection of claims 1-5 has been maintained, as allegedly being anticipated by *Ladner et al.* U.S. Patent 5,223,409 (*Ladner et al.*). Specifically, it is stated that *Ladner et al.* anticipate the instant claim 1 because it teaches methods of displaying binding proteins on the surface of filamentous bacteriophage via nucleic acid sequences including gIII and screening for target molecule binding wherein phagemids and helper phage may be utilized pointing to the abstract; columns 1, 4-12, 15-105, Examples I-XVI; and claims 1-66 of *Ladner et al.*

It is also stated in the Office Action that *Ladner et al.* anticipate claim 2 because it teaches separating bacteriophage expressing binding proteins from the target molecules in columns 10-12, and 93-98. With respect to claim 3 it is stated that it is anticipated because it teaches recovering of separated bacteriophage in columns 10-12, 98-99. As to claim 4 it is alleged anticipated because Ladner et al. teach expressing the binding protein in another

expression system including bacterial spores, and artificial methods, etc. in columns 8, 10, 50-77. Finally, with respect to claim 5, it is alleged in the Office Action that *Ladner et al.* teach utilizing the methods to express antibodies including the Fc portion in columns 15-16.

The Applicants respectfully traverse the rejections because *Ladner et al.*, stated concern is that if a helper phage is used there will be recombination between different DNA's encoding displayed molecules and thus that the genotype/phenotype connection would be lost. This would apply whatever the population source, from controlled mutagenesis or otherwise. When *Ladner et al.* says that "Phagemids may be entirely suitable for developing a gene that causes an IPBD to appear on the surface of phage-like genetic packages" this refers to making a phagemid with the full genome of M13, as discussed in detail in Applicants' previous response.

The disclosure in *Ladner et al.* did not use Bluescript K/S that is mentioned in column 76 and therefore, *Ladner et al.* cannot anticipate the present invention based on this.

Still further, the Office Action alleges that *Ladner et al.* discloses employing pGEM® -3Zf in column 106. Specifically, the Office Action states:

> "the construct comprising gIII-binding domain would be inserted into the multiple cloning site for phage display (i.e. plasmid would then contain only ori and gIII of filamentous bacteriophage; please refer to columns 53-59, section IV.B)"

However, the actual disclosure of *Ladner et al.* does not describe that at all. In relation to column 106 of *Ladner et al.*, pGEM® -3Zf is the STARTING MATERIAL for the construction of a vector that explicitly according to *Ladner et al.* employs gene VIII coat protein (not gene III) as fusion partner. The present invention as claimed employs a gene III capsid protein not the gene VIII coat protein and thus it is novel and not anticipated by the vector construct described in column 106 of *Ladner et al.* for this reason in itself. Furthermore, it is explicit in column 106 of *Ladner et al.* that the signal peptide employed is a filamentous bacteriophage gene VIII signal peptide, the construct created being:

viii-signal-sequence::bpti::mature-viii-coat-protein

The gene VIII signal peptide is a nucleotide sequence derived from filamentous bacteriophage that is other than an origin of replication and a nucleotide sequence encoding a gene III capsid protein and the signal peptide is not a component of the viral capsid protein, being cleaved away. The presence of an additional filamentous bacteriophage component in

addition to the only two permitted in the claim (origin of replication and a nucleotide sequence encoding a gene III protein) prevents *Ladner et al.* from anticipating the present invention.

Applicants note that column 111 and Figure 5 of *Ladner et al.* discuss construction of an alternative M13-MB51 in which M13 gene III signal peptide is fused to the BPTI mature VIII coat protein. Again, there is no gene III capsid protein employed, as required by the present claims, and further the use of gene III signal peptide puts the subject-matter outside of the scope of the present claims. Other filamentous bacteriophage sequences are also present. The constructed plasmid MB51 does not contain only an origin of replication and a nucleotide sequence encoding a gIII of filamentous bacteriophage.

In relation to columns 53-59, section IV. B, as cited in the Office Action, these columns make no mention of phagemid at all. Furthermore, column 56 at the top refers to use of "RF M13" and says the "M13 genome is expandable". As has been previously explained, RF (replicable form) genome contains all the phage genes (not just an origin of replication and a nucleotide sequence encoding a gene III capsid protein) and this section is discussing including a complete phage genome and adding in additional genes.

In view of these differences between the *Ladner et al.* disclosure and the subject-matter as recited by the pending claims, Applicants respectfully submit that *Ladner et al.* cannot properly anticipate any of the pending claims as a matter of law and, therefore, the rejections of the claims over *Ladner et al.* may be properly withdrawn.

2. Bass et al.

Claims 1-3 and 5 stand rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Patent 5,688,666 to inventor Bass et al. *(Bass et al.)*

Paragraph 13 of the Office Action states that *Bass et al* teach methods for selecting novel proteins having altered binding properties comprising producing a library of filamentous bacteriophage, surface displaying a library of mammalian proteins including antibodies wherein each filamentous bacteriophage contains a phagemid comprising nucleic acid encoding the protein. It is further stated that in *Bass et al.*, the only nucleic acid sequences derived from filamentous bacteriophage consists of ori and gene III wherein a helper phage is utilized to package the phagemid. However, as explained in more detail below the *Bass et al* disclosure on which the rejection is based, was added in a continuation-in-part application with a priority date

after the disclosure of the above identified patent application. Therefore, *Bass et al* cannot be properly cited as a prior art reference against the pending claims for its allegedly anticipating disclosure.

Anticipation by *Bass et al* is alleged based on subject-matter in *Bass et al* said to relate to selection of novel proteins employing a library of filamentous bacteriophage surface display a library of growth hormone variants or other mammalian proteins including antibodies. It is stated that the *Bass et al* effective filing date is October 28, 1988. However, none of the subject-matter cited is entitled to a date earlier than December 3, 1990 at best, certainly no date earlier than any of the first three priority dates for the present application (set out below).

This can be seen by analysis of the applications from which *Bass et al* claims benefit is set out in Exhibit A (the first page of Bass et al., attached hereto).

The application that led to the grant of *Bass et al* was filed 14 January 1994 (after the filing date of the present application) as a divisional of 715,300 filed June 14, 1991 (after the five priority applications for the present application). 715,300 was a continuation-in-part of 682,400 filed April 10, 1991 and 621,667 filed December 3, 1990, which was a continuation-in-part of 264,611 filed October 28, 1988.

The present application claims the benefit of the following five priority applications:

Priority 1	GB 9015198.6	filed July 10, 1990
Priority 2	GB 9022845.3	filed October 19, 1990
Priority 3	GB 9024503.6	filed November 12, 1990
Priority 4	GB 9104744.9	filed March 6, 1991
Priority 5	GB 9110549.4	filed May 15, 1991.

The present application also has a PCT filing date of July 10, 1991.

Of the applications from which *Bass et al* claims benefit, only 264,611 filed October 28, 1988 is earlier than all of the priority applications for the present application.

264,611 filed October 28, 1988 contains no disclosure relating to display of any protein on the surface of filamentous bacteriophage. Example 1 employs as one option an expression vector that may contain a phage origin of replication. As explained on page 24 "This vector contains origins of replication for phage and E. coli which allow it to be shuttled between such hosts thereby facilitating mutagenesis and expression." A "phage particle" is mentioned on page

25 as one possible expression vector. However, there is absolutely no disclosure of nor suggestion of employing filamentous bacteriophage particles to display proteins at their surface (which requires both concepts and engineering steps not contemplated in the disclosure of 264,611 filed October 28, 1988).

The next application from which *Bass et al* claims benefit is 621,667 filed December 3, 1990, and this was a continuation-in-part adding some disclosure to the contents of 264,611 filed October 28, 1988. However, December 3, 1990 is after the filing of the first three priority applications for the present application. For subject-matter in the present application entitled to at least the priority of Priority 3 GB 9024503.6 filed November 12, 1990, the contents of Bass 621,667 filed December 3, 1990 are not prior art. Furthermore, any subject-matter filed first by Bass in 682,400 filed April 10, 1991 is not prior art to subject-matter in the present application entitled to at least the priority of Priority 4 GB 9104744.9 filed March 6, 1991.

The present claims are fully entitled to priority entitlement from no later than the filing date of Priority 3 GB9024503.6 filed November 12, 1990 which is earlier than December 3, 1990, the earliest date from which bacteriophage display disclosure in *Bass et al* can possibly benefit.

The following table illustrates disclosure providing basis for the present claims in both the application as filed and Priority 3 GB9024503.6 filed November 12, 1990.

Claim	PCT APPLICATION AS FILED	US APPLICATION AS FILED	THIRD PRIORITY DOCUMENT NOV. 12, 1990
Claim 1	Page 17, lines 44-50, along with the paragraph bridging pages 21 and 22, also page 21, lines 7-10, for the rgdp being filamentous bacteriophage, also the experimental examples, paragraph [0020], Example 24, Figure 26.	Page 37, lines 10-17, along with page 45, lines 12-26, also page 43, line 26, to page 44, line 1, for the rgdp being filamentous bacteriophage, also the experimental examples, the paragraph spanning pages 11 and 12, Example 24, Figure 26A.	Page 10, lines 16-20, along with the paragraph bridging pages 11 and 12, also page 10, lines 35-36, for the virus being filamentous bacteriophage, and the experimental examples, page 25, lines 7-14.
Claim 2	Page 17, line 52 (the first optional additional step); also paragraph bridging pages 21-22.	Page 37, lines 18-19 (the first optional additional step); also page 45, lines 12-26.	Page 10, line 22 (the first optional additional step); also first paragraph of page 12.
Claim 3	Page 18, line 1 (the second optional additional step).	Page 37, line 19 (the second optional additional step).	Page 10, lines 22-23 (the second optional additional step.)
Claim 4	Page 18, lines 1-4 (the third optional additional step), along with page 22, lines 21-24.	Page 37, lines 20-22 (the third optional additional step), along with page 46, lines 14-17.	Page 10, lines 23-25 (the third optional additional step), along with, for example, page 1, lines 7-9, and page 16, lines 10-12.
Claim 5	Page 17, line 31; page 23, lines 33-35.	Page 36, lines 21-22; page 49, lines 1-3.	

In view of the above-discussed priority dates of the *Bass et al* disclosure as compared to the priority dates of the above-identified patent application, *Bass et al* cannot properly be cited as prior art against the pending claims and therefore, the rejection of claims 1-3 and 5 under 35 U.S.C. 102(e) over *Bass et al* may be properly withdrawn and withdrawal is respectfully requested.

C. The Claim Rejections Under 35 USC §103(a) Should Be Withdrawn

Claims 1-5 stand rejected under 35 USC §103(a) allegedly as being obvious over *Bass et al* in view of U.S. Patent 5,534,617 to inventor Cunningham et al. (*"Cunningham et al."*) As

discussed in Section B2 of this response, the *Bass et al* disclosure is not a proper prior art reference to the pending claims because it is filing date is post the priority date of the above-identified patent application. Because, *Bass et al* is not a prior art reference it cannot render the pending claims obvious as a matter of law and therefore, the rejection over *Bass et al* in view of *Cunningham et al* under 35 USC §103(a) may be properly withdrawn and withdrawal is respectfully requested.

CONCLUSION

Applicants believe that the application is in good and proper order for allowance and such allowance is respectfully solicited. The Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below with any questions, comments or suggestions relating to this application. Should any additional fees be required for further prosecution of the above-identified patent application, the Commissioner is authorized to deduct any such fees from Howrey LLP Deposit Account No. 08-3038, referencing the above-identified docket number.

Respectfully submitted,
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Exhibit A

GROWTH HORMONE VARIANTS WITH ALTERED BINDING PROPERTIES

This application is a division of application Ser. No. 07/715,300, filed Jun. 14, 1991 (now abandoned), which is a continuation-in-part of application Ser. No. 07/621,667, filed Dec. 3, 1990 (now abandoned) which is a CIP of U.S. Ser. No. 07/264,611 filed 28 Oct. 1988 (abandoned); and a continuation-in-part of application Ser. No. 07/683,400, filed Apr. 10, 1991 (now abandoned).

FIELD OF THE INVENTION

This invention relates to the preparation and systematic selection of novel binding proteins having altered binding properties for a target molecule. Specifically, this invention relates to methods for producing foreign polypeptides mimicking the binding activity of naturally occurring binding partners. In preferred embodiments, the invention is directed to the preparation of therapeutic or diagnostic compounds that mimic proteins or nonpeptidyl molecules such a hormones, drugs and other small molecules, particularly biologically active molecules, such as growth hormone.

BACKGROUND OF THE INVENTION

Binding partners are substances that specifically bind to one another, usually through noncovalent interactions. Examples of binding partners include ligand-receptor, antibody-antigen, drug-target, and enzyme-substrate interactions. Binding partners are extremely useful in both therapeutic and diagnostic fields.

Binding partners have been produced in the past by a variety of methods including: harvesting them from nature (e.g., antibody-antigen, and ligand-receptor pairings) and by adventitious identification (e.g. traditional drug development employing random screening of candidate molecules). In some instances these two approaches have been combined. For example, variants of proteins or polypeptides, such as polypeptide fragments, have been made that contain key functional residues that participate in binding. These polypeptide fragments, in turn, have been derivatized by methods akin to traditional drug development. An example of such derivitization would include strategies such as cyclization to conformationally constrain a polypeptide fragment to produce a novel candidate binding partner.

The problem with prior art methods is that naturally occurring ligands may not have proper characteristics for all therapeutic applications. Additionally, polypeptide ligands may not even be available for some target substances. Furthermore, methods for making non-naturally occurring synthetic binding partners are often expensive and difficult, usually requiring complex synthetic methods to produce each candidate. The inability to characterize the structure of the resulting candidate so that rational drug design methods can be applied for further optimization of candidate molecules further hampers these methods.

In an attempt to overcome these problems, Geysen (Geysen, *Immun. Today,* 6:364–369 [1985]); and (Geysen et al., *Mol. Immun.,* 23:709–715 [1986]) has proposed the use of polypeptide synthesis to provide a framework for systematic iterative binding partner identification and preparation. According to Geysen et al., *Ibid,* short polypeptides, such as dipeptides, are first screened for the ability to bind to a target molecule. The most active dipeptides are then selected for an additional round of testing comprising linking, to the starting dipeptide, an additional residue (or by internally modifying the components of the original starting dipeptide) and then screening this set of candidates for the desired activity. This process is reiterated until the binding partner having the desired properties is identified.

The Geysen et al. method suffers from the disadvantage that the chemistry upon which it is based, peptide synthesis, produces molecules with ill-defined or variable secondary and tertiary structure. As rounds of iterative selection progress, random interactions accelerate among the various substituent groups of the polypeptide so that a true random population of interactive molecules having reproducible higher order structure becomes less and less attainable. For example, interactions between side chains of amino acids, which are sequentially widely separated but which are spatially neighbors, freely occur. Furthermore, sequences that do not facilitate conformationally stable secondary structures provide complex peptide-sidechain interactions which may prevent sidechain interactions of a given amino acid with the target molecule. Such complex interactions are facilitated by the flexibility of the polyamide backbone of the polypeptide candidates. Additionally, candidates may exist in numerous conformations making it difficult to identify the conformer that interacts or binds to the target with greatest affinity or specificity complicating rational drug design.

A final problem with the iterative polypeptide method of Geysen is that, at present, there are no practical methods with which a great diversity of different peptides can be produced, screened and analyzed. By using the twenty naturally occurring amino acids, the total number of all combinations of hexapeptides that must be synthesized is 64,000,000. Even having prepared such a diversity of peptides, there are no methods available with which mixtures of such a diversity of peptides can be rapidly screened to select those peptides having a high affinity for the target molecule. At present, each "adherent" peptide must be recovered in amounts large enough to carry out protein sequencing.

To overcome many of the problems inherent in the Geysen approach, biological selection and screening was chosen as an alternative. Biological selections and screens are powerful tools to probe protein function and to isolate variant proteins with desirable properties (Shortle, *Protein Engineering,* Oxender and Fox, eds., A. R. Liss, Inc., NY, pp. 103–108 [1988]) and Bowie et al., *Science,* 247:1306–1310 [1990]). However, a given selection or screen is applicable to only one or a small number of related proteins.

Recently, Smith and coworkers (Smith, *Science,* 228:1315–1317 [1985]) and Parmley and Smith, *Gene,* 73:305–318 [1985] have demonstrated that small protein fragments (10–50 amino acids) can be "displayed" efficiently on the surface of filamentous phage by inserting short gene fragments into gene III of the fd phage ("fusion phage"). The gene III minor coat protein (present in about 5 copies at one end of the virion) is important for proper phage assembly and for infection by attachment to the pili of *E. coli* (see Rasched et al., *Microbiol. Rev.,* 50:401–427 [1986]). Recently, "fusion phage" have been shown to be useful for displaying short mutated peptide sequences for identifying peptides that may react with antibodies (Scott et al., *Science* 249:386–390, [1990]) and Cwirla et al., *Proc. Natl. Acad. U.S.A* 87:6378–6382, [1990]) or a foreign protein (Devlin et al., *Science,* 249:404–406 [1990]).

There are, however, several important limitations in using such "fusion phage" to identify altered peptides or proteins with new or enhanced binding properties. First, it has been